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Health and Environmental Effects Profile for Diallate

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR DIALLATE

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16. ABSTRACT

The Health and Environmental Effects Profile for Diallate was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficent data are available. Diallate has been evaluated as a carcinogen. The human carcinogen potency factor (q_1^*) for Diallate is 7.8×10^{-1} (mg/kg bw/day)$^{-1}$ for oral exposure.

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents.The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched."

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

ACKNOWLEDGEMENTS

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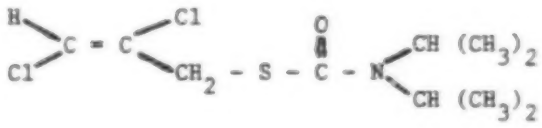
LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
bw	Body weight
GSH	Glutathione
i.p.	Intraperitoneal
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
MTD	Maximum tolerated dose
ppm	Parts per million
s.c.	Subcutaneous
UV	Ultraviolet

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Diallate is the common name for S-2, 3-dichloroallyl diisopropylthiocarbamate. It is also known as dichloroallyl diisopropylthiocarbamate; bis (1-methylethyl) carbamothionic acid, S-(2,3-dichloro-2-propenyl)ester; and 2,3-dichloro-2-propene-1-thiol, diisopropyl carbamate (IARC, 1976). This compound was introduced in the market under the code number "CP 15336" and has a trade name of Avadex. The structure of diallate is given below:



Molecular formula: $C_{10}H_{17}Cl_2NOS$

Molecular weight: 270.2

The Chemical Abstract Service (CAS) Registry Number for this compound is 2303-16-4.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Diallate is a brown liquid at ambient temperature. It exists in two isomeric forms, namely, the cis- and the trans-isomers. Commercial formulations of diallate contain roughly equal amounts of the cis- and transisomers (IARC, 1976). Some of the physical properties of diallate are given below:

Boiling point:	150°C at 9 mm of Hg (IARC, 1976)
Melting point:	
cis-isomer:	<0°C (BCPC, 1977)
trans-isomer:	36°C (BCPC, 1977)
Density:	$d^{25}_{15.6}$ 1.188 (IARC, 1976)
Solubility in water at 25°C:	14 mg/ℓ (BCPC, 1977)
Vapor pressure at 25°C:	1.5×10^{-4} mm of Hg (IARC, 1976)
Evaporation rate at 20°C:	2.87 μg/cm² hr (IARC, 1976)

1.3. PRODUCTION DATA

The compound is prepared by the condensation of diisopropylamine, carbonyl sulfide and 1,2,3-trichloropropene (BCPC, 1977). Diallate is produced by Monsanto Co. at Lubing, LA (SRI, 1982). Production data for the United States are unavailable, but in 1971 the estimated yearly production was <1 million pounds (Lawless et al., 1972).

1.4. USE DATA

Diallate is used as a pre-planting or pre-emergence herbicide in the selective control of wild oats and other weeds in sugar beets, flax, barley, corn, forage legumes, lentils, peas, potatoes, soybeans, root crops, oil crops, and fruit and ornamental trees (IARC, 1976).

2. ENVIRONMENTAL FATE AND TRANSPORT

Although the fate of diallate in soils has been studied extensively, little data regarding its fate and transport in the atmospheric media are available. The two important routes of entry of this herbicide into the atmosphere are spray drift during application and evaporation from soil after application. Like other chemicals in the atmosphere, the fate of diallate in the air is likely to be determined by its ability to react with O_3, NO_x and free radicals (e.g., RO•, O• and RO_2•), and its ability to undergo photochemical reactions. While it is likely that diallate may undergo photochemical reaction with available sunlight in the vapor and aerosol phase (Nassar and Ebing, 1979), the quantitative aspect of this reaction has not been studied. Similarly, the reactivity of diallate with the likely atmospheric molecules or free radicals is not known either qualitatively or quantitatively. Therefore, it is difficult to predict the atmospheric fate of this compound.

The transport of diallate in the atmospheric medium has not been studied. Based, however, on a soil sorption coefficient K_{oc} (adsorption coefficient based on soil organic carbon content) of 170-1900 (Kenaga, 1980; Grover et al., 1979), this compound probably will exist in the atmosphere in the particulate-sorbed phase. Both wet and dry deposition are likely to remove the particulate-sorbed diallate from the atmosphere. Considering the low solubility of this compound (14 mg/ℓ), the latter process is more likely to be the predominant removal mechanism.

The fate and transport of diallate in aquatic media have not been well studied. Both chemical and biological reactions determine the fate of a chemical in aquatic media. Photochemical reactions, free radical reactions and hydrolytic reactions are the three likely classes of chemical reactions

that may determine the fate of this chemical in water. The fact that diallate undergoes a photochemical reaction in the aquatic media is attributed to the investigation of Nassar and Ebing (1979); however, the quantitative nature of this reaction remains unknown. The hydrolysis of triallate, a compound similar to diallate, was studied by Smith (1969). He found very little hydrolysis (only 10-15%) of this compound in 24 weeks between pH 4 and 8. Because diallate may hydrolyze at a slower rate than triallate (Smith and Fitzpatrick, 1970), hydrolysis appears to be an insignificant process for diallate in aquatic media. Although the rates of biodegradation of diallate in aquatic media have not been determined, based on its biodegradability in soils (Smith and Fitzpatrick, 1970), it is possible that biodegradation plays an important role in determining the fate of diallate in this medium.

Two processes that are likely to predominate in the aquatic transport of diallate are sorption and volatilization. The volatility of diallate from aqueous solution was determined by Nassar and Ebing (1979). These authors determined that ~60 and 82% of trans- and cis-diallate, respectively, evaporated from the aquatic phase after 16 days. The adsorption of diallate by soils from aqueous solution by two soil types was determined to be ~70% (Smith and Fitzpatrick, 1970). This result indicates that sorption onto suspended particulate matter with subsequent partial precipitation to the sediment may play a significant role in determining the transport of this compound in aquatic media.

No experimental data regarding the bioconcentration of this chemical by aquatic organisms are available. From binary regression equations, Kenaga (1980) predicted a BCF range for this chemical of 120-140. Therefore, diallate is not expected to bioaccumulate significantly in aquatic organisms.

The fate and transport of diallate in soil has been studied more extensively. The fate of diallate in soils is likely to be controlled by its ability to undergo chemical and biological reactions. The three chemical reactions that may be responsible for the disappearance of this chemical from soil are hydrolysis, radical oxidation and photochemical reaction. Based on the studies of Smith and Fitzpatrick (1970) and Smith (1969), it is unlikely that hydrolysis plays any significant role in determining the fate of this chemical in soil. The significance of free radical reactions of diallate in soils has not been studied. The photolysis of diallate in soil was studied by Nassar and Ebing (1979), who found that this compound decomposed at a higher rate when coated as a film on a glass surface than when incorporated in soil. This is not surprising in view of the fact that more light attenuation is expected when light penetrates beyond the soil surface. Soil containing 4 ppm diallate was irradiated with a sunlamp (spectrum similar to that of natural sunlight) and the irradiation produced 33-36% decomposition of diallate in 16 days. From their experimental results with two different types of soils, Smith and Fitzpatrick (1970) concluded that chemical reactions are insignificant compared to biological reactions for diallate in soils.

Available data indicate that soil microorganisms contribute significantly to the disappearance of diallate incorporated in soils (Kaufman, 1967). It has been shown that an organism, Fusarium oxysporum, isolated from soils can degrade diallate (Kaufman and Blake, 1973). The major route of degradation involved dehalogenation. The significance of diallate biodegradation may depend on the nature of soil (Koren et al., 1968). For example, in soils with extremely low sorptive capacity, volatilization plays such a significant role that microbial degradation assumes a secondary role; however,

in soils with moderate adsorption capacities, the herbicide is subjected to a significant degradation by microorganisms. The half-life for microbial degradation of diallate in soils has been estimated as 28-42 days by Smith and Fitzpatrick (1970) and ~24 days by Anderson and Domsch (1980). The average half-life of diallate in soil when applied at the recommended rate (1.5-3.5 lbs/acre) has been estimated as 30 days (IARC, 1976). In the presence of the insecticide chlorpyrifos, the half-life of diallate in soil may increase substantially depending upon the concentration of added chlorpyrifos (Anderson and Domsch, 1980).

The three important processes that may control the transport of diallate in soils are volatilization, leaching and sorption. The sorption of diallate in soil, which partly controls both volatilization and leaching processes, was studied by a number of investigators (Nassar and Ebing, 1979; Smith and Fitzpatrick, 1970; Kenaga, 1980; Koren et al., 1969; Grover et al., 1979). The stronger the sorption of a chemical in soil, the lower its chances for volatilization. Again, the adsorption constant is directly proportional to the organic content of the soil. Thus, it can be stated qualitatively that volatilization will play a major role in transporting this compound from soils containing low organic carbon (Koren et al., 1968; Kaufman, 1967). The volatility of diallate from soil may also increase following rainfall, probably due to increased soil vapor flux after desorption of the herbicide upon soil wetting (Grover et al., 1981). The only quantitative data regarding the importance of soil volatility of diallate have been provided by Nassar and Ebing (1979). These authors determined that the evaporation of 41.4 and 47.3% of the trans- and cis-diallate, respectively, from soil required 32 days, however, this study failed to prove conclusively that biodegradation had no role in the observed disappearance of this compound from soil.

The leaching of diallate from soil is directly related to its water solubility and inversely related to the organic content of the soil (Koren et al., 1969). Since diallate has a low water solubility and a reasonably high soil adsorption coefficient, this compound may not leach significantly from soils (Smith and Hayden, 1976). In soils containing low organic carbon (<3%), however, some leachings of diallate from soils were observed (Koren et al., 1969).

3. EXPOSURE

No monitoring data for diallate are available in STORET (see Appendix A). The levels of this compound in air, water or food are not available from published literature. Since some plants are known to absorb diallate from soil and translocate it to the aereal parts of the plants (Nalewaja, 1968), it is likely that the residue of this compound will be found in some edible agricultural products. Dubelman et al. (1982) measured the dermal and inhalation exposure of field operators during application of diallate to sugar beets. The total operator exposure for the complete herbicide application sequence to 20-acre plots measured in µg of herbicide/kg bw is given in Table 3-1.

It is obvious from Table 3-1 that dermal deposition was the main contributor to the total exposure to diallate, which can be reduced by almost 2 orders of magnitude by the use of rubber gloves and a closed system for tank fill operations.

TABLE 3-1

Occupational Exposure to Diallate for Complete Application Sequence*

Application System	Inhalation Exposure (µg/kg bw)	Dermal Deposition (µg/kg bw)	Total Exposure (µg/kg bw)
Conventional tank fill + boom spray + disc incorporation	0.37	982.3	982.3
Conventional tank fill + spray/harrow combination	0.55	987.3	987.8
Closed System (Chemprobe) + spray/harrow combination	0.55	10.6	11.2

*Source: Dubelman et al., 1982

4. PHARMACOKINETICS

4.1. ABSORPTION

Specific data on the absorption of diallate were unavailable; however, some information was obtained from excretion data. Marsden and Casida (1982) recovered small amounts of the metabolites of diallate in the 24-hour urine of rats treated with diallate at 100 μmole/kg bw by gavage. Rats receiving oral doses of 0.32-0.65 mg/kg of [^{14}C=O] diallate excreted 74-77% of the radioactivity in the urine and 20% as $^{14}CO_2$ after 30 hours (Chen et al., 1979). These studies indicate that diallate is absorbed from the gastrointestinal tract of rats, but further data regarding plasma levels or the kinetics of absorption were not available.

4.2. DISTRIBUTION

Little information regarding the distribution of diallate was available. Chen et al. (1979) found that, 30 hours following gavage dosing of rats with 0.32-0.65 mg [^{14}C=O] diallate/kg, 0.5% of the administered radioactivity was retained in the liver, 0.3% in the blood, and 1.5-2.0% in other tissues.

4.3. METABOLISM

The metabolism of diallate has been studied in both <u>in vitro</u> and <u>in vivo</u> systems. Diallate was metabolized extensively by liver microsomes from rats or mice but only in the presence of NADPH, indicating an oxidative reaction. The sulfoxide that would result from such a reaction was undetected; however, it was considered to be a highly reactive intermediate (Chen et al., 1979; Schuphan et al., 1979).

The mouse microsomal-NADPH system metabolism of [^{14}C=O] diallate resulted in 49-67% $^{14}CO_2$, 1-3% ^{14}COS (carbonyl sulfide), 4-10% of five unidentified metabolites, and 1-3% protein bound derivatives. In the presence of glutathione (GSH), ~20% less $^{14}CO_2$ was liberated, ^{14}COS levels

increased and ^{14}C-labeled-S-(diisopropyl carbamoyl)-GSH accounted for 28-30% of the radioactivity. Chemical studies indicated that the sulfoxide rather than diallate itself reacts with GSH (Chen et al., 1979; Schuphan et al., 1979). Rats treated orally with [^{14}C=O] diallate excreted ~62% of the radiolabel as mercapturic acid conjugate, 20% as CO_2, 7% as cysteine and 15% as mercaptoacetic acid (Chen et al., 1979; Schuphan et al., 1979).

When [^{14}C-allyl] diallate was incubated with the mouse or rat microsome-NADPH system, the major metabolite was dichloroallylsulfonic acid (probably formed from the sulfoxide). The mouse microsomal-NADPH system also produced 2-^{14}C-chloroacrolein, a potent mutagen (Schuphan et al., 1979).

Based on these observations, the following metabolic pathways were proposed. Sulfoxidation of diallate yields diallate sulfoxide which in the presence of GSH forms the S-diisopropyl-carbamoyl-GSH conjugate, which decomposes to the mercapturic acid conjugate. Dichloroallysulfenic acid, which breaks down to dichloroallylsulfonic acid may also be formed. In the absence of GSH, or in competition with the GSH reaction, diallate sulfoxide decomposes to S-O-allylsulfonate ester (a proposed intermediate), which undergoes 2,3-sigmatropic rearrangement eventually yielding carbamoylsulfenyl chloride and 2-chloroacrolein (Schuphan et al., 1979). An additional pathway was proposed by Chen et al. (1979), based on the finding of carbonyl sulfide as an in vitro metabolite, in which diallate is hydroxylated at the alpha carbon of the 2,3-dichloroallyl group, yielding a proposed alpha hydroxyallyl diallate intermediate which forms carbonyl sulfide, which in turn is oxidized to CO_2.

Marsden and Casida (1982) suggested that 2-chloroacrolein, which appears to be responsible for diallate mutagenicity (Section 5.2.), is unstable and is further metabolized to 2-chloroacrylic acid. Rats given single oral doses of 100 μmole/kg diallate excreted 0.21% of the dose as 2-chloroacrylic acid in 24 hours. When rats were injected i.p. with 10 μmole/kg 2-chloroacrolein, ~0.26% was excreted as the acid. The low recoveries were presumed to be due to the high reactivity of 2-chloroacrolein.

4.4. EXCRETION

As mentioned in Sections 4.1. and 4.3., low levels of 2-chloroacrylic acid were excreted in rat 24-hour urine (Marsden and Casida, 1982). Chen et al. (1979) recovered 74-77% of the radioactivity as urinary metabolites, 20% as $^{14}CO_2$ in the exposed air and 1-3% in the feces of rats within 30 hours after an oral dose of 0.32-0.65 mg/kg of [^{14}C=O] diallate.

5. EFFECTS

5.1. CARCINOGENICITY

Only a few studies regarding the carcinogenicity of diallate were available. Two hybrid strains of mice, $B6C3F_1$ and $B6AKF_1$, were given 215 mg/kg diallate [the maximum tolerated dose (MTD), which was determined from the average body weight of mice and not corrected for weight gain] daily by gavage from day 7 to day 28 of age, after which diallate was given in the diet at levels of 560 ppm for up to ~18 months. Negative controls consisted of untreated and vehicle treated mice of both sexes and both strains. After 84-86 weeks of age, the mice were killed and necropsied. Total tumor incidence for $B6C3F_1$ mice was 14/16 treated males and 5/16 treated females vs. 22/79 control males and 8/87 control females ($p<0.01$ for males, $p<0.05$ for females). Hepatomas were found in 13/16 treated males and 3/16 treated females, compared with 8/79 total negative control males and 0/87 total negative control females ($p<0.01$ for both sexes). Pulmonary tumors were found in 4/16 treated males vs. 5/79 controls ($p<0.05$). For strain $B6AKF_1$, total tumor incidences were 12/18 treated males and 2/15 treated females, compared with 16/90 control males and 7/82 control females ($p<0.01$ for males; p was not significant for females); 10/18 treated males had hepatomas vs. 5/90 total negative controls ($p<0.01$) (Innes et al., 1969; BRL, 1968).

In a meeting abstract, Ulland et al. (1973) reported an increased incidence of tumors in Charles River rats exposed to diallate. In a later and full report of this study, Weisburger et al. (1981) stated that diallate did not increase the tumor incidence. In this study, Charles River rats were fed 300 ppm (MTD) or 150 ppm diallate for 18 months and observed for an additional 6 months. Groups consisted of 26 males and 26 females per dosage level. No increased tumor incidences were found in either sex when compared with either matched or pooled controls.

$B6C3F_1$ and $B6AKF_1$ mice (18 mice/sex/strain) were given one-time s.c. injections of 1000 mg/kg diallate in corn oil on the 28th day of age and killed after 18 months. The incidence of reticulum cell sarcoma was 4/18 in male mice of the $B6C3F_1$ strain compared with 8/141 control males of the same strain ($p<0.05$). Other differences in tumor incidences were not significant (BRL, 1968). Thus, orally administered diallate increased the incidence of liver and other tumors in two strains of mice, but not in rats.

In a 2-year carcinogenicity study conducted at Monsanto Laboratories, Johannsen et al. (1977) administered diallate to groups of 50 male and 50 female rats at dietary concentrations of 0, 50, 100 or 200 ppm. Depressed weight gain was observed in females at the 200 ppm level; food consumption data were not reported. For all dose levels tested, there were no gross pathological changes, and no difference in survival, number of animals with tumors, number of tumors, or number of animals with malignant neoplasms when compared to corresponding control values. Further details of this study were not reported in the proceedings abstract, and no published paper on this study was found. An abstract of a French study (Darnis, 1980) indicated that crop residues of diallate induced liver tumors in mice and rats following oral or s.c. administration. No further details of the study were given in the abstract.

5.2. MUTAGENICITY

Diallate is mutagenic in a variety of assay systems including bacterial, fungal, haploid plant, Drosophila, mouse, rat, hamster and human cell cultures causing reverse mutation, forward mutation, inhibition of DNA synthesis, inducement of unscheduled DNA synthesis, mitotic cross-over, gene conversion, recombination, sister-chromatid exchange and other mutagenic effects. The results of these studies as reported by the authors are

summarized in Table 5-1. For a review of some of these short-term mutagenicity assays see Carere and Morpurgo (1981).

Based on the results of these studies it is concluded that diallate is a mutagen requiring metabolic activation to produce its effects. As stated in Section 4.3., the metabolite considered responsible is 2-chloroacrolein (Schuphan et al., 1979; Chen et al., 1979).

Rosen et al. (1980) studied the functional group requirements for diallate mutagenicity by comparing the mutagenic activity of 2-chloroacrolein, 2-chloroallyl alcohol, 2-chloroallyl acid and other substitutions in the Salmonella typhimurium S-9 system. They proposed a mechanism of mutagenicity for 2-chloroacrolein, whereby the reaction of deoxyadenosine with the difunctional 2-chloroacrolein forms a polymer as a result of Schiff base formation cross-linking at the carbonyl group and Michael addition at the double bond.

5.3. TERATOGENICITY

In a teratogenicity study conducted at Monsanto Laboratories, Johannsen et al. (1977) administered diallate orally to pregnant rabbits at doses of 3 or 10 mg/kg on days 6-18 of gestation. Neither dose level induced a teratogenic response in the offspring of treated dams. Further details of this study, including the presence or absence of maternal toxicity and/or fetotoxicity, were not reported in the proceedings abstract, and no published paper on this study was found.

Ebron and Kitchin (1982) cultured explanted rat embryos with 1.0 or 3.0 mM diallate in 2.5% corn oil, with resultant dysmorphogenesis and retarded growth independent of microsomal action. When diallate was dissolved in 0.1% acetone, these effects were more pronounced than with the corn oil suspension, and the presence of the microsomal system further

TABLE 5-1

Mutagenicity Testing of Diallate

Assay	Indicator Organism	Application	Concentration or Dose	Activating System	Response*	Comment	Reference
Reverse mutation	S. typhimurium (8 strains)	spot test	NR	None	-	Only 3 of 110 herbicides tested gave a weak pusitive response under the conditions of the study.	Andersen et al., 1972
Reverse mutation	S. typhimurium					NC	Carere et al., 1978
	TA1535	spot test	200 µg/plate	None	-		
	TA1536	spot test	200 µg/plate	None	-		
	TA1537	spot test	200 µg/plate	None	-		
	TA1538	spot test	200 µg/plate	None	-		
Reverse mutation	S. typhimurium						Sikka and Florczyk, 1978
	TA1535	plate incorporation	0-500 µg/plate	± S9	±	+ at ≥1 µg/plate ($p<0.05$) with a dose response increase ($p<0.01$)	
	TA1538	plate incorporation	0-500 µg/plate	± S9	-		
	TA98	plate incorporation	0-500 µg/plate	± S9	-		
	TA100	plate incorporation	0-500 µg/plate	± S9	±	+ at ≥5 µg/plate ($p<0.01$) with a dose response increase ($p<0.01$)	
Reverse mutation	S. typhimurium						DeLorenzo et al., 1978
	TA1535	plate incorporation	0-250 µg/plate	± S9	±	+ at ≥10 µg/plate with a dose dependent increase	
	TA1537	plate incorporation	0-250 µg/plate	± S9	-		
	TA1538	plate incorporation	0-250 µg/plate	± S9	-		
	TA98	plate incorporation	0-250 µg/plate	± S9	-		
	TA100	plate incorporation	0-250 µg/plate	± S9	±	+ at ≥10 µg/plate with a dose dependent increase. The response was greater for TA100 than for TA1535.	
Reverse mutation	S. typhimurium						Douglas et al., 1981a,b
	TA1535	plate incorporation	0-10 mg/plate	± S9	±	+ ≥0.001 mg/plate with dose response increased with maximum of 557 revertants/plate at 0.05 mg/plate	
	TA100	plate incorporation	0-10 mg/plate	± S9	±	+ at ≥0.001 mg/plate, reaching 1317 revertants/plate at 0.10 mg/plate	
	TA1537	plate incorporation	0-10 mg/plate	± S9	-		
	TA1538	plate incorporation	0-10 mg/plate	± S9	-		
	TA98	plate incorporation	0-10 mg/plate	± S9	±	+ at ≥0.005 mg/plate - max of 143 revertants/plate at 0.5 mg/plate	
Reverse mutation	S. typhimurium	NR	NR	rat liver S-9	+	The response with frog liver S9 was less than that with rat liver S9. Further details were not given in the abstract.	Cheh et al., 1980
				frog liver S-9	+		

TABLE 5-1 (cont.)

Assay	Indicator Organism	Application	Concentration or Dose	Activating System	Response*	Comment	Reference
Reverse mutation	S. typhimurium TA100	NR	NR	± S9	±	Five strains were tested, but the two strains that gave negative results were not specified, nor were further details available from the abstracts.	Sandhu et al., 1981
	TA98			± S9	±		Kasica et al., 1981
	TA1535			± S9	±		
Reverse mutation	Saccharomyces cerevisiae	NR	NR	± S9	-	Further details were not given in the abstracts.	Sandhu et al., 1981; Kasica et al., 1981
Reverse mutation	Escherichia coli	NR	NR	NR	-	Further details were not given in the abstracts.	Sandhu et al., 1981; Kasica et al., 1981
Forward mutation	Streptomyces coelicolor	spot test	400 µg/plate	None	+	MC	Carere et al., 1978
Forward mutation	Aspergillus nidulans	NR	NR	NR	+	The abstract indicated that diallate was among the tested chemicals that were mutagenic to A. nidulans.	Morpurgo et al., 1977
Mitotic cross-over	S. cerevisiae D_7	NR	NR	± S9	±	Details of the studies were not given in the abstracts.	Sandhu et al., 1981; Kasica et al., 1981
Mitotic gene conversion	S. cerevisiae D_7	NR	NR	± S9	±	Details of the studies were not given in the abstracts.	Sandhu et al., 1981; Kasica et al., 1981
Mitotic recombination	S. cerevisiae D_7	NR	NR	NR	+	Details of the studies were not given in the abstracts.	Sandhu et al., 1981; Kasica et al., 1981
Mitotic recombination	S. cerevisiae D_3	NR	NR	NR	+	Details of the studies were not given in the abstracts.	Sandhu et al., 1981; Kasica et al., 1981
Growth inhibition	Pelargonium zonale	one drop to terminal bud	10^{-3} M	NR	+	Mutation rate was 6-8 times higher than control rate.	Pohlheim et al., 1977
Sex-linked recessive lethal	Drosophila melanogaster	NR	NR	NR	+	Further details were not given in the abstracts.	Sandhu et al., 1981; Kasica et al., 1981
Thymidine kinase	mouse lymphoma L5178y	cell culture	NR	± S9	±	Further details were not given in the abstracts.	Sandhu et al., 1981; Kasica et al., 1981
Inhibition of DNA synthesis	rat thymus cells	cell culture	0-1000 µg/mL	NR	+	+ at ≥10 µg/mL (2% inhibition of ^{3}H TdR uptake)	Rocchi et al., 1980

TABLE 5-1 (cont.)

Assay	Indicator Organism	Application	Concentration or Dose	Activating System	Response*	Comment	Reference
Chromosome aberrations	Chinese hamster ovary (CHO) cells	cell culture	0-3.25 x 10^{-4} M	+ S9	+	+ at $\geq$2 x 10^{-4} with abrupt and steep dose response	Douglas et al., 1981a,b
Sister chromatid exchange	CHO cells	cell culture	0-4 x 10^{-4} M	+ S9	+	+ at $\geq$1 x 10^{-4} with a dose response increase	Douglas et al., 1981a,b
DNA damage	CHO cells	cell culture	0-5 x 10^{-4} M	+ S9	+	+ at $\geq$1 x 10^{-4} with dose response increase	Douglas et al., 1981a,b
Cytotoxicity	CHO cells	cell culture	0-5 x 10^{-4} M	+ S9	+	+ at $\geq$1 x 10^{-4} with dose response decrease in % survival	Douglas, et al., 1981a,b
Inhibition of DNA synthesis	human lymphocyte cells	cell culture	500 µg/ml	NR	+	68% inhibition of scheduled DNA synthesis	Rocchi et al., 1980
DNA repair after UV damage	human lymphocyte cells	cell culture	500 µg/ml	NR	+	75% inhibition of unscheduled DNA synthesis induced by UV damage	Rocchi et al., 1980
Unscheduled DNA synthesis	human embryo EUE cells	cell culture	0-3.6 x 10^{-3} M	NR	+	+ at $\geq$3.6 x 10^{-4} with dose response	Benigni and Dogliotti, 1980a,b; Benigni et al., 1982
Dominant lethal	male mice	i.p. injection	100 or 200 mg/kg	None	-	NC	Johannsen et al., 1977

*Responses: +, positive; -, negative; =, negative with and without S9 activation system; ±, positive with and negative without S9 activation system

NC = No comment; NR = not reported

enhanced the embryotoxicity of diallate. The concentrations of corn oil or acetone were not embryotoxic in preliminary experiments.

5.4. OTHER REPRODUCTIVE EFFECTS

In a multi-generation reproductive study that was in progress at Monsanto Laboratories, Johannsen et al. (1977) reported that no treatment-related effects were seen in rats fed diallate at dietary concentrations of 30 or 100 mg/kg over two generations. Further details of this study were not reported in the proceedings abstract, and no published paper on this study was found.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

In a 2-year chronic oral toxicity study conducted at Monsanto Laboratories, Johannsen et al. (1977) administered diallate to groups of 50 male and 50 female rats at dietary concentrations of 0, 50, 100 or 200 ppm. Depressed weight gain was observed in females at the 200 ppm level; food consumption data were not reported. For all dose levels tested, there were no gross pathological changes and no effect on hematologic indices, clinical chemistry, urinalyses, absolute organ weights or organ weight ratios when compared to corresponding control values. Further details of this study were not reported in the proceedings abstract, and no published paper on this study was found.

The only other available data regarding the toxicity of diallate upon chronic or subchronic exposure were reported in abstracts of Russian studies. Gzhegotskii and Doloshitskii (1971) exposed rabbits and guinea pigs chronically to dermal or ocular applications, s.c. injections or peroral dosing with diallate resulting in local irritation, weight loss and hematological changes. Details of dose concentration or duration of exposure were not specified in the abstract.

Doloshitskii (1969) reported an 8-month experiment in which it was determined that 5 mg/kg diallate was the threshold for toxic action, producing altered motor chronaxy and cholesterol concentrations in rats, while doses of 0.5 mg/kg produced no effect. No further experimental details were reported in the abstract.

5.6. OTHER RELEVANT INFORMATION

Ben-Dyke et al. (1970) reported oral LD_{50} values of 393-1000 mg/kg diallate for rats and dermal LD_{50} values of 2000-2500 mg/kg for rabbits. Doloshitskii (1969) reported LD_{50} (route unspecified) values for diallate of 1000 mg/kg for rats and 420 mg/kg for guinea pigs. The Pesticide Index (Wiswesser, 1976) reported an oral LD_{50} for diallate of 510 mg/kg for dogs.

In an abstract of a Russian study, Pestova (1966) reported an oral LD_{50} value of 860 mg/kg diallate for mice and 1267 mg/kg for rats, with observed effects of tearing, salivating, panting, excitement changing to depression within 10-15 minutes, and convulsions.

6. AQUATIC TOXICITY

6.1. ACUTE TOXICITY

Alabaster (1969) reported that the 24-hour LC_{50} for diallate was 12 ppm for harlequin fish, Rasbora heteromorpha. Gzhegotskii et al. (1971) indicated that crucian carp and guppies were killed by 5 mg/ℓ of diallate.

6.2. CHRONIC TOXICITY

Pertinent data regarding chronic effects of diallate were not located in the available literature.

6.3. PLANT EFFECTS

Hess (1980) reported that growth of algae, Chlamydomonas eugametos, was completely inhibited by exposure to diallate at 27 mg/ℓ, but no effects were observed at 2.7 mg/ℓ.

6.4. RESIDUES

Pertinent data regarding diallate residues were not located in the available literature.

6.5. OTHER RELEVANT INFORMATION

Pertinent data regarding other relevant information on diallate were not located in the available literature.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

According to the Federal Register (FR), the EPA has published position documents on diallate (U.S. EPA, 1980a) and has proposed to cancel or deny registration for all uses involving emulsifiable concentrates since its social, economic and environmental benefits are overshadowed by its carcinogenic risk [45(112) FR 38437-38440].

According to the Code of Federal Regulations (CFR), the tolerance for diallate on alfalfa, barley, flaxseed, lentils, peas, pea forage and hay, potatoes, safflower seeds, soybeans and sugar beets was established as 0.05 ppm under the Federal Food, Drug and Cosmetic Act (40 CFR 180.277). The recommended maximum permissible concentration of diallate in water supplies in the USSR is 0.03 mg/ℓ (Doloshitskii, 1969).

7.2. AQUATIC

Guidelines or standards for the protection of aquatic organisms from the toxic effects of diallate have not been derived.

B. RISK ASSESSMENT

Only a few animal studies have been performed to assess the carcinogenic potential of diallate. These studies include a chronic 84-week study in which males and females of two strains of mice were given diallate, first by gavage (215 mg/kg) for 3 weeks, followed by 560 ppm diallate in the diet for 81 weeks. Liver tumors were induced in male mice of one strain and in both sexes of the other strain (BRL, 1968; Innes et al., 1969). In two reports of a chronic feeding study (Ulland et al., 1973; Weisburger et al., 1981), diallate was given at 0, 150 or 300 ppm in the diet for 18 months followed by 6 months of observation. In the preliminary report (Ulland et al., 1973) an increased incidence of tumor-bearing treated rats was found when compared with controls, while in the Weisburger et al. report no significant differences in tumor incidence were observed. In addition, a study in mice given single s.c. injections of 1000 mg/kg diallate reported an increased incidence of reticulum cell sarcomas in males of one strain when necropsied 18 months later (BRL, 1968).

Although the evidence for diallate carcinogenicity is limited to these few studies, the many positive mutagenicity studies in *in vitro* bacterial assays (Sikka and Florczyk, 1978; Cheh et al, 1980; Sandhu et al., 1981; DeLorenzo et al., 1978; Douglas et al., 1981a; Carere et al., 1978), in a *Drosophila melanogaster in vivo* assay (Sandhu et al., 1981), and in rodent and human cell culture assays (Rocchi et al., 1980; Douglas et al., 1981a; Benigni et al., 1982) support a potential carcinogenic action for diallate. The U.S. EPA has proposed to cancel or deny the registration for all uses of the emulsifiable concentrate of diallate because of its potential carcinogenic risk [45(112) FR 38437-38440].

Thus, since diallate or a metabolite of diallate has been considered to be carcinogenic, the data from the chronic oral study in mice (BRL, 1968; Innes et al., 1969) can be used to estimate a cancer risk level. Assuming that a mouse consumes the equivalent of 13% of its body weight/day as food, the dose for the dietary portion of this study was 72.8 mg/kg/day. The time-weighted average dose for the entire study period (dietary and gavage) was then calculated to be 78 mg/kg/day. Based on the hepatoma response of male $B6C3F_1$ mice (13/16 treated vs. 8/79 control mice) and using the linearized multistage model developed by Kenneth Crump and adopted by the U.S. EPA (1980b), a carcinogenic potency factor (q_1^*) of 7.77×10^{-2} $(mg/kg/day)^{-1}$ can be derived for humans. The corresponding dose associated with an increased lifetime cancer risk of 10^{-5} is 1.29×10^{-5} mg/kg/day, or 9.03×10^{-4} mg/day for a 70 kg man. Complete data for derivation of the q_1^* are presented in Appendix B.

Statements concerning available literature in this document refer to published, quotable sources and are in no way meant to imply that confidential data, which this document could not address, are not in existence. These data, which are considered Confidential Business Information (CBI), are available in summary form as a CBI Appendix that can be accessed by individuals with appropriate clearance. Conclusions from the CBI Appendix regarding risk assessment can, however, be presented in this chapter.

The CBI Appendix to this document reviews other animal studies one of which supplies additional evidence of the carcinogenicity of diallate. Syrian golden hamsters fed diallate in the diet had increased incidences of melanomas, relative to controls. Tentatively, using the EPA proposed guidelines for carcinogen risk assessment, diallate would be classified as a Group B2 compound, meaning that it is probably carcinogenic in humans.

Using the dose-response data from this study, the U.S. EPA (1982) calculated a q_1^* of 6.10×10^{-2} $(mg/kg/day)^{-1}$. The q_1^* based on the data of Innes et al. (1969) remains the more conservative value for risk assessment.

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APPENDIX A

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
MEDLINE
RTECS
SCI SEARCH
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
EPCASR
Chemical Industry Notes

Most of these searches were conducted in February, 1983; a few were conducted March-May, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 7 and 8th), and the following secondary sources were reviewed:

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APPENDIX B

Cancer Data Sheet for Derivation of q_1^*

Compound: Diallate

Reference: Bionetics Research Laboratories (BRL, 1968); Innes et al. (1969)

Species, Strain, Sex: mice, B6C3F1, males

Body Weight: 0.040 kg (measured)

Length of Exposure (l_e) = 588 days

Length of Experiment (L_e) = 588 days

Lifespan of Animal (L) = 730 days (assumed)

Tumor Site and Type: liver, hepatoma

Route, Vehicle: oral: by gavage in corn oil for 21 days, then in diet for 567 days

Experimental Doses or Exposures	Transformed Dose (mg/kg/day)	Incidence No. Responding/ No. Tested (or Examined)
0	0	8/79
215 mg/kg/day x 21 days, then 560 ppm (diet) x 567 days	78	13/16

Human $q_1^* = 7.77 \times 10^{-1}$ $(mg/kg/day)^{-1}$

10^{-5} risk level = 1.29×10^{-5} mg/kg/day = 9.03×10^{-4} mg/day for 70 kg man